REMARKS

Claims 1,2,7 and 8 were elected for prosecution. Amended claims 1,2,7 and 8 are under consideration. Reconsideration is respectfully requested.

Applicant has submitted amended process claims 9 and 10 , which are submitted for consideration for rejoinder with product claims 1and 2, in the event claims 1 and 2 are allowed.

Election/Restriction

Applicant has elected to prosecute claims in Group I, i.e., claims 1, 2, 7 and 8 drawn to the composition of an EEIIMDI polypeptide and a fibrinolytic agent, and method of enhancing the fibrinolytic activity of said agent, classified in class 424, subclass 94.64. Claims 3-6 are cancelled.

Specification

The Action has objected to the abstract because it recites material not presently elected. The Action has reproduced the following sections of MPEP 608.01(b) entitled "GUIDELINES FOR THE PREPARATION OF PATENT ABSTRACTS", parts A, B and C.

In response, the Abstract and Specification has been amended.

The Action has characterized as verbose, under 35 U.S.C. 112, first paragraph, the use of the terms "docking "site in paragraph [0001] and "a finger domain" in paragraph [0023].

In response, applicant disagrees. The above two terms are used by artisans skilled in the art and are not in any way unclear. See Ref cited Under 35 USC 103- Zhang et al., page

27053, col2 line 13. To amend the above terms would be a mistake.

The Action has also rejected paragraphs 17, 18 and 55 as having informalities, in particular in the term EEIIMD.

In response, applicant has amended paragraphs 17, 18 and 55 to correct the mistakes. This rejection should be withdrawn.

Claim Rejections Under 35 U.S.C 112, first paragraph.

The Action rejected claims 1, 2, 7 and 8 as failing to comply with the enablement requirement, and would require undue experimentation under In re Wands 858 F.2d 731,737, 8 USPQ 1400,1404 (Fed Cir 1988). Specifically the Action states that *"The breath of claims 1 and 2 (and 7 and 8) reads on a composition comprising the polypeptide EEIIMD and a fibrinolytic agent, specifically scuPA, in amounts capable of inducing fibrinolytic activity without causing hemorrhage."*

In response, claims 1 and 7 are amended to more specifically state the range of dosage used for the peptide EEIIMD. Claims 2 and 8 are dependent of Claims 1 and 7 respectively, and are therefore amended too.

The Action states *"The specification discloses a method for decreasing the vasoactivity associated with the fibrinolytic agents tPA and TNK-tPA (Example 3), but discloses no examples drawn to enhancing the fibrinolytic activity of scuPA by administering the polypeptide EEIIMD. By applicant's own admission, "the peptide of the present invention has no effect on the fibrinolytic activity of scuPA" (paragraph 30).*

In response, applicant disagrees with the Action's conclusion that *"the peptide of the present invention has no effect on the fibrinolytic activity of scuPA".* This statement is part of a statement that stating that while preventing and/or inhibiting the adverse effects of scuPA on blood

vessels, the peptide has no such effect on the fibrinolytic activity of scuPA. This is NOT a new interpretation because, the sentence that follows supports it- that the peptide is useful in clot lysis during thrombolytic therapy (with scuPA- since the paragraph deals with scuPA). Applicant has amended paragraph to more particularly clarify that the peptide does not have a preventive or inhibitory effect on scuPA's fibrinolytic activity.

The Action States:

A regimen is disclosed for administering alteplase with the peptide EEIIMD, but said regimen does not suggest conditions for any other plasminogen activator including scuPA (paragraphs 32 , 33). The disclosure recites a preferred dosage regiment for said peptide: " an amount effective to optimally enhance the activity of the fibrinolytic activity[sic] while also preventing the harmful vasoactive effects of a fibrinolytic agent on a case by case basis" (paragraph 34). Said regimen cannot be interpreted to be applicable to scuPA, however, as applicant has explicitly stated that said peptide does not enhance the activity of scuPA. Additionally it is not clear whether the phrase "case by case" refers to individual patients, diagnoses, situations, conditions, peptides or fibrinolytic agents. In any case, applicant has provided insufficient guidance for a person of ordinary skill in the art to have reasonable expectation of success in using the claimed invention.

In response, applicant disagrees. As indicated by the examiner, there was a typographical mistake and [activity] should have been "agent". And accordingly it is fibrinolytic "agent" that applicant is referring to when using the statement "case by case". Applicant has amended paragraph 34 to make this correction.

The Action states that:

None of the working examples are drawn to co-administration of the EEIIMD peptide with scuPA or any uPA. While a narrow working embodiment cannot be a sole factor in determining enablement, its limited showing, in light of the unpredictable nature of the art and the lack of direction provided by the applicant, provides additional weight to the lack of enablement in consideration of the Wands factors as a whole. Thus, one of ordinary skill in the art would not have a reasonable expectation of success in using the claimed invention."

In response, applicant disagrees with the above conclusion. Applicant refers the examiner to Figure 1A sheet ¼, in which a combination of scuPA and EEIIMD is shown to produce enhanced fibrinolytic activity.

Rejection Under 35 U.S.C.112, second paragraph.

Claims 1, 2, 7 and 8 were rejected for failing to set forth the subject matter of the invention, because of the difference in recitation of the sequence EEIIMD and EEIIMI.

Applicant has corrected the mistake by deleting EEIIMI, and amended claims 1 and 7 to provide actual amounts of effective amount of the peptide, and indicating that the hemorrhage is cranial.

The Action states *" Claim 7 is drawn to "a method of enhancing thrombolytic activity of a fibrinolytic agent by administering an effective amount of polypeptide EEIIMD and a fibrinolytic agent to induce the desired level of fibrinolytic activity without causing hemorrhage." It is not clear from the language of the claims under which conditions said peptide and agent are to be administered, and no process steps are provided to describe the manner in which said peptide and agent should be administered. ..The words "effective" and desired" fail to describe specifically what the end product of the method is.*

In response, applicant has provided in claims 1 and 7 the conditions in which the polypeptide may be administered. The word "effective" has been used to indicate the therapeutic dosage, and the word "desired" has been used to indicate the required level of fibrinolytic activity that does not cause hemorrhage. These words have been used commonly in pharmaceutical inventions in patent law.

As to the requirement of "process steps" that describe how the peptide will be administered is not required under the patent law, because these steps are usually worked out in clinical studies. Under In re Brana, "usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer." 51 F.3d 1560, 34 USPQ 1436 (Fed. Cir 1995).

Rejection Under 35 U.S.C. 103

The Action rejected claims 1, 2, 7 and 8 under 35 USC 103(a) as being unpatentable over U.S. Patent No 5,130,143 (Ref A in IDS) in view of Zhang et al (J.Biol Chem 272: 27053, 1997) (Ref U in IDS).

The Action states:

"U.S. '143 teaches a combination of the fibrinolytic agent uPA and low molecular weight heparin (LMW-heparin) that binds it and a method of co-administering uPA and LMW-heparin to dissolve

bloot clots while reducing the risk of hemorrhage (Example 6 and column 7, line 42 through column 9, line 35. US '143 also teaches that the binding of heparin inhibits some protease activities of plasminogen activators (Figure 1). US '143 does not teach the co-administration of uPA with the peptide EEIIMD.

Zhang et al teach the peptide EEIIMD, the sequence of which is derived from the uPA regulator PA-1. PA-1 and the peptide EEIIMD bind to various forms of uPA (ie scuPA and tcuPA, p 27053). Zhang et al also teach that PAI-1 inhibits protease activity of plasminogen activators."

In response, applicant disagrees. As described in the cited section form U.S. '143, LMW-heparin is used to bind the uPA, to inhibit the protease activity and thus reduce the risk of hemorrhage. This is quite the opposite of the present invention. The present invention adds the peptide EEIIMD to scuPA to increase the proteolytic activity. And in spite of the increase in scuPA activity, there is decreased hemorrhage because of inhibition of uPA associated vasoactivity by EEIIMD. Clearly, US '143 teaches away from the present invention. As the Action states, US'143 does not teach co-administration of uPA and the peptide EEIIMD.

As to Zhang et al. this reference describes how EEIIMD stimulated the binding of scuPA to purified ά2 MR/LRP-associated proteins but not of tcuPA. It is important to note that applicant Abd Al-Roof Higazi is a co-author in this study. There is no teaching or suggestion in this paper that EEIIMD had an enhancing effect on scuPA's fibrinolytic activity. This is a recent discovery. In the study described in Zhang et al EEIIMD was being studied as the amino acid 350-355 in PAI -1 designated as the "docking site". See line 13, column 2 of page 27053.

Examiner's conclusion that "Zhang et al also teach that PAI-1 inhibits protease

activity of plasminogen activators" teaches away from the present invention. This is because in the present invention, the peptide EEIIMD is not mimicking the inhibitory effect on uPA proteolytic activity, but is actually enhancing scuPA's fibrinolytic activity. There is therefore no basis to combine US '143 and Zhang et al, because each reference teaches away from the present invention.

Applicant refers to MPEP 2141.02 and specifically points out that in determining the differences between the prior art and the claims, the question under 35 USC 103, is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. Stratoflex, Inc. v. Aeroquip Corp. 713 F. 2d 1530 218 USPQ 871 (Fed. Cir. 1983).

The Federal Circuit, in reference to references cited in an obviousness rejection, has held that:"The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention."Hodosh v. Block Drug Co., Inc., 786 F.2d 1136, 1143 n.5, 1986 MPEP 2141. Moreover, the prior art reference must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable. Expectation of success must be found in the prior art, and not based on applicant's disclosure. In re Vaeck 947 F. 2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991) (MPEP §2143). Therefore, as a matter of fact and law, there is no basis to sustain the rejection of claim1 1, 2, 7 and 8. This rejection should be withdrawn.

Applicant has made diligent effort to amend the claims and respond to points made in the Office Action. If for any reasons however, the Examiner should deem that this application is not in condition for allowance, the Examiner is respectfully requested to telephone the undersigned attorney listed below to resolve any outstanding issues prior to

issuing a further Office Action.

Respectfully submitted,

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BY Rashida A. Karmali

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